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EDITORIAL COMMENT

# Prediction scores for risk of allograft loss in patients receiving kidney transplants: nil satis nisi optimum

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## ABSTRACT

Long-term graft survival is the main concern of kidney transplantation. Some strategies have been tested to predict graft survival using estimated glomerular filtration rate or proteinuria at different time points, histologic assessment, non-invasive biomarkers or even machine-learning methods. However, the 'magical formulae' for allograft survival prediction does not exist yet.

**Keywords:** graft function, graft survival, kidney transplantation, prognosis

The main concern of both kidney transplant (KT) clinicians and recipients has been always long-term graft survival. Being able to estimate a predicted graft survival would be a relevant improvement to predict outcomes for individual patients not only for advising, but also for identifying, those for whom interventions could be beneficial.

Some strategies have been tested to find a unique good earlier predictor, but there are many factors involved in long-term graft survival. In the past, 1-year estimated glomerular filtration rate (eGFR) was the most used outcome in clinical trials since it is a good surrogate marker for long-term graft survival [1, 2]. In this issue of *Clinical Kidney Journal*, Mottola *et al.* [3] address an important issue for the prediction of long-term graft survival based on eGFR and proteinuria in transplant recipients. They conducted a prospective study including 754 patients using a validation cohort of 1936 individuals evaluating if an early and easy marker such as eGFR and proteinuria at 3 months can predict hard outcomes. The authors conclude that both parameters were powerful predictors for kidney allograft loss, concluding that early outcomes may be useful to early interventions.

It is difficult to obtain such a simplistic model of prediction of graft survival, taking into account that it is the result of multiple factors such as cold ischaemia time [4], delayed graft function [4], ischaemic preconditioning, type of donor [5, 6], donor and recipient age [7, 8], recipient immunological risk, HLA matching, acute rejection episodes or post-transplant host factors [9]. However, although all these factors are associated with renal allograft loss, few have been found to have high predictive value for individual patients (Figure 1).

In the past, preimplantation biopsy was used to evaluate the potential 'capacity' of a kidney allograft and some groups implemented the strategy of dual kidney transplantation or even discarded the organ based on this histologic score [10]. But the reports published to date, including a substantial number of biopsies, are of poor quality, heterogeneous, retrospective and show contradictory results [10–13]. Subsequent histological evaluation of the allograft during follow-up is

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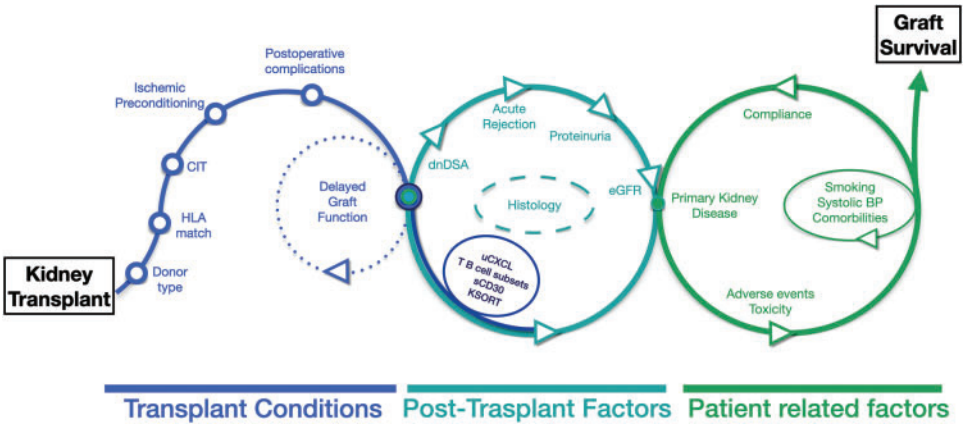


**FIGURE 1:** Factors related to allograft survival. BP: blood pressure; CIT: cold ischaemia time.

routinely performed in many centres to detect signs of subclinical rejection, drug toxicity or presence of glomerular disease recurrence [14, 15]. Therefore, this evaluation can potentially give information about the prognosis.

Standardized immune monitoring constitutes a part of usual clinical practice. It is widely known that the presence of *de novo* donor-specific anti-HLA antibodies (dnDSA) is associated with acute antibody-mediated rejection (AMR) and allograft loss. But of all patients with dnDSA, only those with histologic evidence of acute, active AMR either at DSA detection or on subsequent biopsy had an increased incidence of graft failure and/or 50% reduction in eGFR [15]. Identification and performance analysis of non-invasive biomarkers such as mRNA and miRNA expression profiles, chemokines or changes in immune cell subsets in either blood or urine of renal transplant patients would be a valuable methodology of prediction graft survival. The problem is that biomarker research projects falter at the validation or replication stage and in the end they have shown low positive predictive value, with difficulties in standardization [16]. At the moment, some urinary chemokines are being investigated to predict renal function outcomes: urinary CXCL9, CXCL10 and miR-210 levels are related to an increased rejection risk and decrease of renal function [17–19]. Other molecules such as serum soluble CD30 (a costimulatory molecule for activated T lymphocytes) have been described to be associated with worse allograft outcome [20], and when it is combined with DSA measurements the graft-survival prediction improves [21] in some reports. Gene expression studies, especially DNA microarray technology, have led to identification of various genes potentially associated with renal transplant outcome such as TRIB1, miR-142-5p or a combination of genes such as the kidney solid organ response test [22, 23]. Another potential tool is the analysis of blood T- and B-cell subsets, for example, increased numbers of blood $T_{reg}$ cells and their increased FOXP3 expression in long-term stable renal recipients is associated with good outcome [24].

However, there are other factors that potentially contribute to allograft loss. Some recipient characteristics, such as primary kidney disease, have a direct effect on allograft survival. Chronic kidney disease patients usually have cardiovascular risk factors and other comorbidities. Also, immunosuppression treatments are related to secondary effects with a direct harmful effect on cardiovascular risk factors such as hypertension, hyperglycaemia or hyperlipidaemia, increased risk of infections or obesity. These diseases usually contribute to the progression of native kidney disease, but their effect on allograft survival is less known. It is necessary to consider that graft survival censored for death, the outcome evaluated in the majority of observational studies, assumes that patients who died would have had the same risk of graft loss as those who did not. It would be more accurate to perform a risk analysis accounting for death as a competing event of graft failure. In competing risk analyses, smoking, systolic blood pressure and haemoglobin remained independent predictors of graft failure or doubling of creatinine (an endpoint indicating worsening of graft function) [9, 25].

Therefore, many prediction systems for risk of allograft loss based in machine-learning methods could be a potential solution to considering all these factors. Several models have been published , and 39 of them have also been systematically reviewed [26] (Table 1). The most recent one is the iBox [27], based on a multicentric French study including 4000 KT recipients validated with a European and North American cohort. This tool evaluates functional, histological, immunological allograft parameters and HLA antibody profiling. The major advantage over the previously published scores is that it can be performed irrespective of the time point after transplantation and it can be re-evaluated at any time to assess the effect of any intervention.

Despite the scientific interest in developing sophisticated tools for prediction, there is some scepticism as to their clinical utility. Prediction tools use past or current variables to generate prediction models that work at the population level. However, as transplant care is a dynamic process with many unanticipated decisions, this prediction will lose accuracy for a specific individual. For example, one can imagine what is going to happen in an ideal scenario such as young kidney donor in an HLA haploidentical recipient. Any machine-learning method would predict a very long-term graft survival, but what if this recipient is under immunosuppressed by a doctor's decision or by a simple misunderstanding? Complex models can even anticipate non-adherent profiles but definitively fail to identify clinical practice variability.

The whole transplant community would find it very useful to have a 'magical formula' to show them exactly until when a given allograft will be viable, which would facilitate the development of therapeutic strategies to decrease the risk for severe clinical events and mortality. However, for the transplant community, as for the Everton FC fans, 'nil satis nisi optimum', which means 'nothing but the best is good enough'.

**Table 1. Published prediction scores for graft survival in KT population**

| Reference, model name | Population study, period | Variables included in the model | C-statistics (prediction of graft survival) |
|---|---|---|---|
| Based on pre-transplant information | | | |
| Molnar *et al.* [28] TransplantScore | $n = 15\,125$, July 2001 to June 2006 | Recipient: age, race, type of insurance, primary cause of ESRD, diabetes, hemoglobin, duration on dialysis + donor: diabetes + number HLA mismatches | 0.63 (95% CI 0.60–0.66) |
| Kasiske *et al.* [29] | $n = 59\,091$, 2000–06 | Donor age, history of hypertension + recipient: age, race, insurance, duration on dialysis, cause of ESRD, HCV antibody, trauma as cause of death | 0.66 (95% CI 0.64–0.69) |
| Based on post-transplant information | | | |
| Loupy *et al.* [27], iBox | $n = 4000$, 2005–14 | Recipient: demographics, characteristics of transplant, allograft functional parameters, immunological parameters, allograft + time of post-transplant risk evaluation, allograft functional parameters (eGFR and proteinuria), allograft histological parameters | 0.81 (95% CI 0.79–0.83) |
| Fournier *et al.* [30], Dynamic prediction of Patient and Graft survival' (DynPG) | $n = 1637$, January 2007 to December 2017 | Recipient: age, graft rank, cardiovascular histories, pre-transplantation anti-HLA Class I immunization, SCr at 3 months, occurrence of acute rejection in the first year post-transplantation | At 1 year = 0.72 (95% CI 0.64–0.76)At 6 years = 0.76 (95% CI 0.64–0.88) |
| Gonzales *et al.* [31] | $n = 1465$, January 1999 to December 2008 | Birmingham risk model recipient factors at the first year (age, sex, ethnicity, renal function, proteinuria, prior acute rejection) + histologic findings at 1-year surveillance biopsy+serum donor-specific alloantibody status | 0.90 (95% CI 0.85–0.95) |

CI: confidence interval.

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## CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously.

## REFERENCES

1. Kasiske BL, Israni AK, Snyder JJ *et al.* The relationship between kidney function and long-term graft survival after kidney transplant. *Am J Kidney Dis* 2011; 57: 466–475
2. Hariharan S, McBride MA, Cherikh WS *et al.* Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int* 2002; 62: 311–318
3. Mottola C, Girerd N, Duarte K *et al.* Prognostic value for long-term graft survival of the estimated glomerular filtration rate and proteinuria quantified at 3 months after kidney transplantation. *Clin Kidney J* 2020; 13: 791–802
4. Quiroga I, McShane P, Koo DDH *et al.* Major effects of delayed graft function and cold ischaemia time on renal allograft survival. *Nephrol Dial Transplant* 2006; 21: 1689–1696
5. Locke JE, Segev DL, Warren DS *et al.* Outcomes of kidneys from donors after cardiac death: implications for allocation and preservation. *Am J Transplant* 2007; 7: 1797–1807
6. Cohen JB, Potluri V, Porrett PM *et al.* Leveraging marginal structural modeling with Cox regression to assess the survival benefit of accepting vs declining kidney allograft offers. *Am J Transplant* 2019; 19: 1999–2008
7. Pérez-Sáez MJ, Montero N, Redondo-Pachón D *et al.* Strategies for an expanded use of kidneys from elderly donors. *Transplantation* 2017; 101: 727–745
8. Peters-Sengers H, Berger SP, Heemskerk MBA *et al.* Stretching the limits of renal transplantation in elderly recipients of grafts from elderly deceased donors. *J Am Soc Nephrol* 2017; 28: 621–631
9. Wekerle T, Segev D, Lechler R *et al.* Strategies for long-term preservation of kidney graft function. *Lancet* 2017; 389: 2152–2162
10. Wang CJ, Wetmore JB, Crary GS *et al.* The donor kidney biopsy and its implications in predicting graft outcomes: a systematic review. *Am J Transplant* 2015; 15: 1903–1914
11. Remuzzi G, Cravedi P, Perna A *et al.* Long-term outcome of renal transplantation from older donors. *N Engl J Med* 2006; 354: 343–352
12. De Vusser K, Lerut E, Kuypers D *et al.* The predictive value of kidney allograft baseline biopsies for long-term graft survival. *J Am Soc Nephrol* 2013; 24: 1913–1923
13. Carta P, Zanazzi M, Caroti L *et al.* Impact of the pre-transplant histological score on 3-year graft outcomes of kidneys from marginal donors: a single-centre study. *Nephrol Dial Transplant* 2013; 28: 2637–2644
14. Enderby C, Keller CA. An overview of immunosuppression in solid organ transplantation. *Am J Manag Care* 2015; 21 (1 Suppl): s12–s23
15. Schinstock CA, Cosio F, Cheungpasitporn W *et al.* The value of protocol biopsies to identify patients with de novo

donor-specific antibody at high risk for allograft loss. *Am J Transplant* 2017; 17: 1574–1584
16. Willis JCD, Lord GM. Immune biomarkers: the promises and pitfalls of personalized medicine. *Nat Rev Immunol* 2015; 15: 323–329
17. Hricik DE, Nickerson P, Formica RN *et al.*; for the CTOT-01 consortium. Multicenter validation of urinary CXCL9 as a risk-stratifying biomarker for kidney transplant injury. *Am J Transplant* 2013; 13: 2634–2644
18. Rabant M, Amrouche L, Morin L *et al.* Early low urinary CXCL9 and CXCL10 might predict immunological quiescence in clinically and histologically stable kidney recipients. *Am J Transplant* 2016; 16: 1868–1881
19. Lorenzen JM, Volkmann I, Fiedler J *et al.* Urinary miR-210 as a mediator of acute T-cell mediated rejection in renal allograft recipients. *Am J Transplant* 2011; 11: 2221–2227
20. Susal C, Dohler B, Sadeghi M *et al.* Posttransplant sCD30 as a predictor of kidney graft outcome. *Transplantation* 2011; 91: 1364–1369
21. Grenzi PC, Campos EF, Tedesco-Silva H *et al.* Association of high post-transplant soluble CD30 serum levels with chronic allograft nephropathy. *Transpl Immunol* 2013; 29: 34–38
22. Danger R, Sawitzki B, Brouard S. Immune monitoring in renal transplantation: the search for biomarkers. *Eur J Immunol* 2016; 46: 2695–2704
23. Crowley LE, Mekki M, Chand S. Biomarkers and pharmacogenomics in kidney transplantation. *Mol Diagn Ther* 2018; 22: 537–550
24. Alvarez CM, Opelz G, Garcia LF *et al.* Expression of regulatory T-cell-related molecule genes and clinical outcome in kidney transplant recipients. *Transplantation* 2009; 87: 857–863
25. Holme I, Fellstrom BC, Jardine AG *et al.* Model comparisons of competing risk and recurrent events for graft failure in renal transplant recipients. *Clin J Am Soc Nephrol* 2013; 8: 241–247
26. Kabore R, Haller MC, Harambat J *et al.* Risk prediction models for graft failure in kidney transplantation: a systematic review. *Nephrol Dial Transplant* 2017; 32 (Suppl 2): ii68–ii76
27. Loupy A, Aubert O, Orandi BJ *et al.* Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. *BMJ* 2019; 366: l4923
28. Molnar MZ, Nguyen DV, Chen Y *et al.* Predictive score for posttransplantation outcomes. *Transplantation* 2017; 101: 1353–1364
29. Kasiske BL, Israni AK, Snyder JJ *et al.* A simple tool to predict outcomes after kidney transplant. *Am J Kidney Dis* 2010; 56: 947–960
30. Fournier M-C, Foucher Y, Blanche P *et al.*; DIVAT Consortium. Dynamic predictions of long-term kidney graft failure: an information tool promoting patient-centred care. *Nephrol Dial Transplant* 2019; 34: 1961–1969
31. Gonzales MM, Bentall A, Kremers WK *et al.* Predicting individual renal allograft outcomes using risk models with 1-year surveillance biopsy and alloantibody data. *J Am Soc Nephrol* 2016; 27: 3165–3174